REMARKS

Claims 1-13 and 15-19 are pending, with claims 7, 8, 12, 13, 18 and 19, being withdrawn from consideration. Claim 1 is amended herein. No new matter is introduced by way of the amendments to the claims. Support for the amendments can be found, for example, on pages 6, and in the Examples and Figures, as originally filed. Applicants respectfully request entry of the amendments and reconsideration of the claims in view of the remarks below.

Double patenting

Claim 1 is provisionally rejected over claim 10 of copending application no. 10/535047. To the extent that the Examiner believes that this rejection should be maintained with respect to the amended claims, Applicants respectfully request that the rejection be held in abeyance until such time as one or the other application is in condition for allowance or until the double patenting rejection is the only rejection remaining in the application.

Claims 1-6, 9-11 and 15-17 are non-obvious

Claims 1-6, 9-11 and 15-17 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Chien *et al.* (US 6261764, "Chien") in view of Glenn *et al.* (US2006/0199174, "Glenn"), and in certain cases Shah *et al.* (US 6727092, "Shah"). To the extent that the rejection is maintained with respect to the amended claims, Applicants traverse.

Under 35 U.S.C. § 103, a patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support he legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.* (550 U.S. ___, 127 S. Ct. 1727, 2007, 82 USPQ2d 1385, 1396).

Where the Examiner alleges that the claimed invention is a combination of prior art elements according to known methods, the Examiner must articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between

> the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference:
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
> Federal Register Vol. 72, No. 195: 57256, at 57529.

"If any of these findings cannot be made, then this rationale *cannot* be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.* (emphasis added)

Thus, a proper rejection under 35 USC § 103 requires that the Examiner 1) identify prior art that differs from the claimed subject matter only in a way that would have been obvious at the time the invention was made; and 2) to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

The current claims are directed to immunogenic compositions capable of eliciting an HCV-specific T cell response that include a first expression cassette comprising a polynucleotide sequence that encodes an HCV Core protein and a second expression cassette comprising a polynucleotide sequence that encodes at least one other HCV protein, wherein the first and second expression cassettes cause expression of the Core protein and the at least one other HCV protein within the same cell, wherein the first expression cassette encoding the Core protein is in a cis location downstream of the second expression cassette that encodes at least one of the other HCV proteins. Such immunogenic compositions are demonstrated to elicit an HCV-specific immune response characterized by a robust T cell response.

As discussed in the response filed on 15 September 2008, the currently claimed immunogenic compositions include 1) a first expression cassette comprising a polynucleotide sequence encoding the HCV core protein that is located downstream from 2) a second expression cassette encoding at least one other HCV protein. Applicants respectfully submit that such immunogenic compositions are both novel and non-obvious with respect to the cited references, as explained in more detail below.

First, Chien simply does not disclose or suggest any immunogenic compositions, much less compositions that are established to elicit a T cell response specific for HCV. Second, Chien does not even disclose any compositions comprising a first expression cassette encoding the HCV core protein that is downstream from a second expression cassette encoding at least one other HCV protein.

Rather, Chien concerns the field of immunoassays, specifically anti-HCV immunoassays (column 1 of Chien, field of invention). Chien discloses a number of HCV antigens used in combination with disclosed diluents and buffers in the context of manual or automatic assays (column 4, lines 48-54). Included in this list of antigens is MEFA-6, highlighted by the examiner. The MEFA-6 construct is a single cassette containing epitopes from the core, envelope, NS3, NS4 and NS5 regions of the HCV polyprotein (Column 5, lines 12-15), which results in the high level production of a single multiple-epitope fusion antigen. In view of the high level of production reported by Chien, the skilled person would not be taught or motivated to alter the means of expressing this antigen as there is no problem associated with its expression. In addition, it is known in the art that expressing proteins in more than one expression cassette can result in lower expression of the second cassette, as well as additional problems such as recombination between the cassettes.

Thus, Chien fails in a number of respects to teach the instantly claimed immunogenic compositions. Firstly, Chien teaches polynucleotide constructs useful for producing proteins *in vitro*, not immunogenic compositions that elicit a T cell response *in vivo*. Second, Chien teaches a construct with a single expression cassette that is capable of producing high levels of the HCV polyprotein. Nothing in Chien discloses the use of HCV antigens in immunogenic compositions or suggests that there is any reason, in the context of such an immunogenic composition to provide the nucleic acids that encode the HCV proteins in two distinct expression cassettes.

The Examiner states that Glenn (US2006/0199174) discloses "that single and dual expression cassette vectors are well known in the art [0073 of Glenn]." Glenn discloses such vectors for the purpose of expressing NSB4 nucleotide binding motif polypeptides, see e.g., [0064] of Glenn. Paragraph [0113] of Glenn mentions immune response-stimulating compositions which contain virus particles containing polynucleotides encoding polypeptides having an NS4B nucleotide binding motif. Applicants do not contest that both single and dual vectors were known in the art. However, the Examiner

points to nothing in Glenn that discloses or suggests immunogenic compositions containing the HCV core protein and at least one other HCV protein (even the aforementioned NS4B). Thus, Glenn provides nothing that teaches or suggests with any specificity that in an immunogenic composition including both an HCV Core protein and a nonstructural protein, such as the NS4B protein discussed by Glenn, or any other nonstructural protein, should be expressed using two different expression cassettes arranged in cis, with the polynucleotide encoding the Core protein being specifically situated downstream of the other HCV protein. Thus, Glenn does not provide the basis for modifying any constructs taught by Chien to produce the immunogenic composition of instant Claim 1 (and claims dependent therefrom).

Nor does Shah remedy the deficiencies of Chien and Glenn. As discussed in detail in the Response filed 15 September 2008, Shah relates to HCV diagnostic tests, and does not provide any teachings concerning the immunogenic compositions that are capable of eliciting an HCV specific T cell response *in vivo*. Furthermore, like Chien, a single plasmid, with the coding sequences for a nonstructural protein (in this case NS3) and Core being within a single expression cassette, was used to express the recombinant antigen. Therefore, Shah does not provide any teaching or suggestion that a dual promoter, in the specific arrangement instantly claimed, be used to express Core and at least one nonstructural protein in the context of an immunogenic composition to elicit an HCV-specific T cell response.

None of the cited reference, alone or in any combination, teach or suggests an immunogenic composition capable of eliciting an HCV-specific T cell response that includes: a first expression cassette comprising a polynucleotide sequence that encodes an HCV Core protein and a second expression cassette comprising a polynucleotide sequence that encodes at least one other HCV protein. None of the cited references even provides a teaching or suggestion that the Core protein rather than a different HCV protein be selected to be expressed in a different expression cassette from the other proteins. Furthermore, even if one elected to place the Core protein in a different expression cassette, there is nothing in the cited references that teaches or suggests that arranging the Core protein cassette downstream of the expression cassette encoding the other HCV protein. In the absence of any teaching or suggestion that addressed these important differences between the subject matter of Claim 1 (and claims dependent

therefrom) and the cited references, it cannot fairly be said that the cited references render obvious the instantly claimed invention.

Furthermore, as discussed in the Response filed 15 September 2008, the particular order in which the cassettes are inserted in the vector is shown in the instant specification to yield surprising and beneficial results. Nothing in any of the cited references lead to the prediction or expectation that, in the specific context of a DNA based immunogenic composition that includes polynucleotides that encode both the HCV Core protein and at least one other HCV protein, arrangement of a first expression cassette encoding the Core protein in a cis location downstream of the second expression cassette that encodes at least one of the other HCV proteins results in substantially higher expression than when the cassettes are provided in the alternative orientation. This unexpected and beneficial consequence of the instantly claimed immunogenic compositions demonstrates that the subject matter of claims 1-5, 15 and 16 is non-obvious, and Applicants respectfully request that the rejection be withdrawn.

Conclusion

Applicants respectfully submit that claims 1-6, 9-11 and 15-17 are allowable in view of the above remarks. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is requested to call the undersigned at the number below prior to the preparation of any further written action. Applicants reserve the right to prosecute subject matter in the originally filed claims, or any other claims supported by the specification in one or more continuing patent applications.

Respectfully submitted,

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